

Interactive Effects of Naturalistic Drinking Context and Alcohol Sensitivity on Neural Alcohol Cue-Reactivity Responses

Jorge S. Martins , Bruce D. Bartholow, M. Lynne Cooper, Kelsey M. Irvin, and Thomas M. Piasecki 

Background: Considerable evidence indicates that a low level of subjective response to alcohol's acute effects (i.e., low sensitivity) is associated with enhanced risk for alcohol use disorder (AUD). Recent work suggests that the highest risk response profile consists of blunted sensitivity to alcohol's sedation-like effects, coupled with enhanced sensitivity to alcohol's stimulation-like effects (i.e., differential sensitivity). A largely separate body of work indicates that enhanced reactivity to alcohol-related cues is associated with increased AUD risk.

Aims: The current research examined the extent to which variability in alcohol response phenotypes is associated with enhanced P3 event-related potential (ERP) responses to alcohol-related pictures (ACR-P3), and whether this reactivity varies according to depicted drinking contexts.

Methods: Eighty young adults (aged 18 to 33 years) completed a self-report measure of alcohol sensitivity (the Alcohol Sensitivity Questionnaire) and viewed images depicting drinking in naturalistic contexts, alcohol and nonalcohol beverages in isolation (devoid of naturalistic drinking context), and neutral nonbeverage control images while ERPs were recorded.

Results: Results indicated that blunted sensitivity to alcohol's sedative-like effects was differentially associated with enhanced ACR-P3 but reduced P3 reactivity to nonalcohol cues. Variation in sensitivity to alcohol's stimulant-like effects was not associated with differential ACR-P3. Contrary to predictions, these effects were not potentiated by drinking contexts.

Conclusions: The current results replicate and extend previous work linking low alcohol sensitivity with enhanced incentive salience for alcohol-related cues and suggest that cues depicting drinking contexts are less likely to differentiate high-risk from low-risk drinkers.

Key Words: Alcohol Sensitivity, Cue Reactivity, Incentive Salience, Social Context, event-related potentials.

DECADES OF RESEARCH have demonstrated substantial interindividual variability in alcohol's acute pharmacological and subjective effects (e.g., Sher and Wood, 2005). This variability has been linked to differential risk for the development of problematic drinking and alcohol use disorder (AUD), such that a low level of subjective response (i.e., low sensitivity; LS) to alcohol is a potent diathesis for these problems (e.g., Morean and Corbin, 2010; Newlin and Thomson, 1990; Pollock, 1992; Quinn and Fromme, 2011). Alcohol sensitivity, sometimes termed subjective response to alcohol, has been proposed as a potential endophenotype through which genetic factors exert their influence on underlying risk for AUD (e.g., Ray et al., 2010; Salvatore et al., 2015; Schuckit, 2018). Attesting to its importance as an

etiologic construct, subjective response or alcohol sensitivity has been proposed as a research domain criterion related to AUD (e.g., Bujarski et al., 2017; Kwako et al., 2016; Litten et al., 2015; Ray et al., 2016).

Theorists have proposed several mechanisms linking LS to heavy drinking and AUD. At a descriptive level, LS individuals are at increased risk for AUD because they must consume relatively large amounts of alcohol to attain desired subjective effects (Schuckit and Smith, 2001; Trela et al., 2016). Additionally, some social, cognitive, and motivational factors, such as associating with heavy-drinking peers (Schuckit et al., 2005, 2016), forming positive alcohol outcome expectancies (e.g., Schuckit et al., 2005), and drinking to cope with stress (Schuckit et al., 2005), have been posited to encourage heavier drinking among LS drinkers, thereby increasing their AUD risk.

Emerging evidence showing enhanced reactivity to alcohol-related cues among LS individuals, relative to their higher-sensitivity (HS) peers, suggests an alternative mechanism, in that LS might reflect enhanced susceptibility to alcohol-related incentive salience sensitization. The incentive sensitization theory of addiction (e.g., Berridge, 2007; Berridge and Robinson, 2016; Robinson and Berridge, 1993)

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proposes that the repeated use of drugs can sensitize brain mesolimbic dopamine circuits to drug-induced reward, especially in large amounts and particularly among genetically and physiologically vulnerable individuals, leading to over-attribution of incentive salience to contextual cues that predict drug ingestion. Drug-related cues thereby acquire incentive motivational properties likely to trigger exaggerated “wanting” responses, as well as conscious desires (i.e., craving) to obtain and consume the drugs.

Importantly, recent research has demonstrated substantial interindividual variability in susceptibility to incentive salience sensitization, which manifests as differences in reactivity to drug-related cues (Flagel et al., 2009; Robinson et al., 2014). Preclinical research using animal models has identified a *sign-tracking* phenotype, characterized by conditioned approach and appetitive responses to reward-predictive cues (e.g., Flagel and Robinson, 2017; Flagel et al., 2008; Robinson et al., 2014) as opposed to reward delivery (i.e., *goal-tracking*; Robinson and Flagel, 2009).

Recent laboratory studies have shown that, among LS drinkers, alcohol cues appear to elicit conditioned appetitive motivational responses reminiscent of sign-tracking. Specifically, among LS drinkers such cues capture selective attention (Shin et al., 2010), trigger approach motivational behavior (Fleming and Bartholow, 2014), instigate feelings of craving (KA Fleming and BD Bartholow, unpublished data), interfere with other ongoing task-relevant goals (Bailey and Bartholow, 2016; Fleming and Bartholow, 2014), and elicit neurophysiological responses indicative of enhanced motivational significance (Bartholow et al., 2007, 2010). Moreover, real-world contexts associated with drinking trigger greater feelings of craving, long considered a feature of problematic substance involvement (see Sayette, 2016), in LS relative to HS individuals (Trela et al., 2018).

However, extant research demonstrating heightened alcohol cue reactivity (ACR) among LS individuals has been limited in some respects. For instance, subjective response profiles are known to differ in terms of the types of subjective effects people experience and the doses of alcohol typically associated with those effects (e.g., Bujarski et al., 2017). Whereas some models posit that AUD risk is primarily associated with a general blunting of response to alcohol (Schuckit, 1980), other models hold that the greatest risk is conferred by a *differential response* profile, consisting of *decreased* sensitivity to alcohol’s sedating effects and *increased* sensitivity to alcohol’s stimulating effects (Newlin and Thomson, 1990; also see King et al., 2011a, 2011b, 2014, 2016). Typically, alcohol’s stimulating effects are associated with relatively lower doses and emerge relatively early in a drinking episode, as blood alcohol concentration (BAC) is increasing, while its sedating effects often are associated with larger doses and emerge later, while BAC is falling (Martin et al., 1993). No previous research has examined whether the increased ACR profiles observed among LS drinkers are

associated with reduced sensitivity to alcohol’s sedation-like effects, enhanced sensitivity to alcohol’s stimulation-like effects, or both. Characterizing the nature of this association will extend our understanding of the neurobiological predispositions or vulnerabilities underlying different alcohol sensitivity phenotypes. In addition, it will allow us to elucidate their potential as a trait marker of heightened susceptibility to alcohol-related incentive salience sensitization, which has important implications for understanding treatment efficacy and relapse risk (Berridge and Robinson, 2016). That is, specifying links between alcohol sensitivity and ACR has the potential to reveal neurobiological mechanisms linking LS with heightened risk for AUD, which could suggest more specific targets for prevention and intervention in this at-risk population.

In addition, existing research examining the association between LS and ACR—and the literature on cue reactivity more generally—is limited by the fact that cues are almost never presented in meaningful drinking contexts. In most studies, including those in which validated alcohol cue stimulus sets are used (e.g., Fey et al., 2017; Pronk et al., 2015; Stauffer et al., 2017), images of alcoholic beverages are presented against a plain (often solid white) background (see López-Caneda and Carbia, 2018, for a recent exception). Although this approach helps to ensure that basic visual properties (e.g., perceptual complexity; brightness and contrast) are equivalent across stimulus types, such stimuli fail to represent the kinds of environments in which people typically encounter and consume alcohol. Presenting alcohol-related cues in naturalistic social contexts might be particularly important when examining ACR responses among young adults, for whom social network factors are especially important in determining alcohol involvement (e.g., Delucchi et al., 2008).

Both theory and research suggest that presenting cues in common drinking contexts could enhance their motivational significance (see Bartholow et al., 2018; Groefsema et al., 2016; Nees et al., 2012), which should potentiate ACR. Indeed, 1 previous study showed that pictures of people drinking (vs. alcohol cues alone) led to decreased startle reflex magnitude in abstinent alcohol-dependent patients compared with healthy controls (Nees et al., 2012), suggesting that alcohol-related cues presented in social contexts are associated with a more pleasant, approach-oriented motivational state (Lang et al., 1990) in AUD patients. Other work suggests that “active” alcohol cues (i.e., pictures of people drinking) elicit greater early attention processing, within 150 ms after cue onset, than do “passive” alcohol cues (i.e., beverages without people) in heavy-drinking young adults (Dickter et al., 2014). Given that affiliation with heavy-drinking peers has been proposed as a mechanism linking LS with increased AUD risk (Schuckit et al., 2005, 2016), it could be that alcohol cues presented in a social context are particularly likely to exacerbate ACR among LS individuals. To our knowledge, this possibility has never been tested.

Overview of the Current Study and Hypotheses

The current study examined the extent to which variability in 2 alcohol response phenotypes (i.e., sensitivity to lower-dose/stimulating effects and blunted sensitivity to higher-dose/sedating effects) is associated with enhanced ACR, as well as whether this reactivity varies according to the contexts in which cues are presented. Participants viewed images representing 1 person drinking (OP; One Person) or more than 1 person drinking (MP; More Than One Person), in addition to nonalcoholic beverages (NA; Nonalcohol) and alcoholic beverages (OA; Only Alcohol) devoid of any naturalistic drinking context. Alcohol response phenotypes were assessed using a retrospective, self-report measure of alcohol sensitivity, the Alcohol Sensitivity Questionnaire (ASQ; Fleming et al., 2016), which permits derivation of scores reflecting sensitivity to lower-dose/stimulating effects and sensitivity to higher-dose/sedating effects.

Individual differences in ACR were quantified using the amplitude of the P3 (or P300) component of the event-related potential (ERP). The P3 is elicited by any attended stimulus (see Polich, 2012), and its amplitude provides a neurophysiological marker of the motivational significance of that stimulus (e.g., Begleiter et al., 1983; Franken et al., 2011; Nieuwenhuis et al., 2005). Its etiologic relevance for AUD has been demonstrated by research showing that P3 amplitude elicited by alcohol cues (ACR-P3) is a robust predictor of alcohol use and heavy drinking (e.g., Bartholow et al., 2007; Little et al., 2012).

Based on recent research suggesting that a differential alcohol response profile conveys the greatest risk for AUD (King et al., 2011a, 2011b, 2014), the most basic prediction advanced for the current study, derived from previous results (Bartholow et al., 2007, 2010), was that ACR-P3 amplitude would be enhanced by differential alcohol sensitivity phenotypes. That is, we predicted that ASQ scores reflecting enhanced sensitivity to lower-dose/stimulating effects and/or blunted sensitivity to higher-dose/sedating effects would be associated with the greatest ACR-P3. Finally, based on the idea that drinking contexts might enhance the motivational significance of alcohol cues among vulnerable individuals, we predicted that ACR-P3 would be most pronounced, particularly among individuals with enhanced sensitivity to lower-dose/stimulating effects or blunted sensitivity to higher-dose/sedating effects, in response to alcohol-related images including people drinking in naturalistic drinking contexts, especially those including multiple people.

MATERIALS AND METHODS

Participants

Ninety-two university undergraduates participated in the study in exchange for research credit in an Introductory Psychology course. Participants were selected from a pool of more than 2,000 undergraduates who completed a web-based pretesting survey containing measures of alcohol use, alcohol sensitivity, and drinking motives. As part of a larger program of research examining

correlates of drinking motives, participants from this pretest sample who indicated they drink primarily to enhance positive experiences (i.e., enhancement motives; $Mean_{\text{enhancement}} = 3.21$, $SD = 0.85$) or to cope with negative affect (i.e., coping motives; $Mean_{\text{coping}} = 1.83$, $SD = 0.79$) were oversampled for participation to ensure the representation of the full range of these motivations, given the high skewness typically observed in these variables. Both distributions of social motives ($Mean_{\text{social}} = 3.47$, $SD = 0.92$) and conformity motives ($Mean_{\text{conformity}} = 1.51$, $SD = 0.63$) in the current study are in line with what typically found in previous studies (see Cooper et al., 2016; Mackinnon et al., 2017). Descriptive statistics indicated a normal distribution of ASQ subscale scores in this sample. Individuals were excluded if they were younger than 18 years of age, had a history of neurologic disease, or had a hairstyle or skin sensitivity contraindicating EEG recording.

Participation of 9 individuals was discontinued for the following reasons: no alcohol consumption in the past year ($n = 1$), history of multiple head injuries ($n = 2$), and problems in the EEG recording ($n = 6$). Data from 3 additional participants were excluded as a result of noncompliance with instructions during the experimental task ($n = 2$) and an excessive number of artifact-contaminated trials in the EEG recording ($n = 1$). The final sample included data from 80 participants, composing a mostly female (58.8%) and predominantly White sample (90%) with ages ranging from 18 to 33 years ($M_{\text{age}} = 19.15$ years, $SD = 2.34$).

Measures and Materials

Alcohol Sensitivity. Individual differences in sensitivity to a wide range of alcohol's effects were measured with the 15-item ASQ (Fleming et al., 2016). The first 9 items query effects of alcohol often associated with lighter drinking and stimulation (e.g., "Do you ever feel high or 'buzzed' after drinking alcohol?"). For each of these items, respondents are asked to indicate whether they have ever experienced the effect from drinking alcohol, and if so, to estimate the minimum number of drinks they must consume in order to experience it. The 6 remaining items assess effects most often associated with heavier drinking and sedation (e.g., "Do you ever pass out after drinking alcohol?"); these items are structured similarly, except that respondents estimate the maximum number of drinks they can consume without experiencing each effect.

Given that the number of items endorsed correlates with the number of drinks reported on each item (see Lee et al., 2015), ASQ scores were computed using a standardized person-mean imputation approach. Specifically, ASQ summary scores were computed as the average of the standardized (i.e., z -score transformed) number of drinks reported for all endorsed effects, such that higher ASQ summary scores indicate lower alcohol sensitivity. Due to dramatic sex differences ($M_{\text{male}} = 6.01$ vs. $M_{\text{female}} = 3.93$, $t(78) = -5.85$, $p < 0.001$), ASQ summary scores were computed separately for men and women, as in previous reports (Bartholow et al., 2010; Shin et al., 2010) and, therefore, a higher ASQ score reflects a higher number of drinks required to experience the effects relative to same-sex peers.

Previous work (Fleming et al., 2016) has confirmed a 2-factor structure for the ASQ, with the 9 items tapping lighter-drinking effects forming 1 factor (ASQ-L; $\alpha = 0.90$) and the 6 items tapping heavier-drinking effects forming another (ASQ-H; $\alpha = 0.95$). Within-factor interitem correlations were $r = 0.54$ for ASQ-L and $r = 0.77$ for ASQ-H. Previous research also supports the construct validity of the ASQ in that scores predict subjective responses to an acute dose of alcohol (Fleming et al., 2016) and do so as well as or better than scores on the more widely used Self-Rating of the Effects of alcohol form (SRE; Schuckit et al., 1997). Specifically, higher ASQ scores (i.e., LS) in terms of light-dose/stimulating-like alcohol's effects were associated with more stimulation when the BAC was rising (i.e., ascending limb of the BAC), whereas higher ASQ

scores in terms of higher-dose/sedating-like alcohol's effects were associated with less sedation when the BAC was declining (i.e., descending limb of the BAC).

Typical Alcohol Use. Typical quantity and frequency of alcohol use were measured using 1 item querying the number of occasions on which participants drank alcohol in the past 12 months (responses ranging from "1 to 5 times" to "Every day," and an option for "Did not drink in the past 12 months"), and a second item querying the typical number of drinks consumed per occasion (responses ranging from "1 drink" to "12 or more drinks"). Responses were coded to reflect typical numbers of drinks per week over the past year. Quantity and frequency of alcohol use were highly correlated ($r = 0.57$); a product term was created reflecting a measure of quantity \times frequency of alcohol use (AlcQF).

Alcohol Picture-Viewing Task. ACR-P3 was elicited in the context of a picture-viewing oddball task (adapted from Bartholow et al., 2007, 2010). The task used here included pictures from 5 different categories: alcoholic beverages without people (e.g., a glass of beer); enhancement-related drinking (e.g., a happy person drinking in a social setting, such as a party); coping-related drinking (e.g., a depressed person drinking at a bar); nonalcoholic beverages (e.g., a glass of orange juice); and neutral images (e.g., a chair). Images from all categories but neutral were found through online searches; the neutral images were the same used in previous studies (see Bartholow et al., 2007, 2010) and were taken from the International Affective Picture System (IAPS; Lang et al., 2008), such that the distribution of the valence ratings was around the midpoint and the arousal ratings were at the low end of the respective scales (Lang et al., 2008).

For the purpose of testing the current study's hypotheses, the beverage pictures were grouped into 4 distinct categories: (i) alcoholic beverages in isolation ($n = 8$ pictures; Only Alcohol [OA]); (ii) nonalcoholic beverages in isolation ($n = 8$ pictures; Nonalcohol [NA]); (iii) 1 person drinking (i.e., a single individual with an alcoholic beverage; $n = 10$ pictures; One Person [OP]); and (iv) more than 1 person drinking (i.e., 2 or more persons with alcohol; $n = 6$ pictures; More Than One Person [MP]) (see Fig. 1).

On each trial of the picture-viewing task, 5 different pictures were presented sequentially, each for 1,000 ms, with jittered interstimulus

intervals of 900, 1,050, or 1,200 ms. At least 4 of the images in each trial sequence were neutral (i.e., context images), and the remaining image (i.e., the oddball target) represented 1 of the 4 picture categories. Thus, the global probability of beverage-related images was 16%. The target image always appeared in the fourth or fifth position in each 5-picture sequence, varying randomly. Following each trial, the word "PAUSE" appeared in the center of the screen for 1,000 ms prior to initiation of the next trial. Participants were instructed to evaluate each image as either neutral or pleasant via button press; response mapping was counter-balanced across participants.

Participants completed a total of 160 5-picture trials (800 picture presentations). The 160 trials were divided into 4 randomly ordered blocks of 40 trials each (participants rested for 5 minutes following the second block). In each block, 32 of the trials contained a target image; the remaining 8 trials contained no targets (i.e., were comprised of all neutral images). This method, along with varying the target position within each trial sequence, helps to reduce anticipatory neural responses that could affect target-elicited P3 responses.

Self-Assessment Manikin. Participants used the Self-Assessment Manikin (SAM; Bradley and Lang, 1994) to rate the images. Each image was rated on separate 9-point scales, 1 for valence (1 = *smiling/happy* to 9 = *frowning/unhappy*) and 1 for arousal (1 = *excited/wide-eyed* to 9 = *relaxed/sleepy*). Ratings of valence and arousal were reverse-coded so that higher scores indicated more positive valence and higher arousal, respectively. Results from ancillary analyses using the valence and arousal ratings are presented in the Appendix S1.

Electrophysiological Recording and Data Processing

The electroencephalogram (EEG) was recorded continuously from 31 tin electrodes (FP1, FP2, F3, Fz, F4, FCz, C3, Cz, C4, T7, T5/P7, CP3, CP1, CPz, CP2, CP4, T8, T6/P8, P3, P1, Pz, P2, P4, PO5, PO3, POz, PO4, PO6, O1, Oz, and O2) fixed in an electrode cap (Electro-Cap International, Eaton, OH) arranged according to the extended 10 to 20 electrode positioning system. Two additional bipolar electrodes were placed above and below the left eye to record blinks, and 2 more were placed at the outer canthi to record



Fig. 1. Exemplar pictures for the 4 distinct target categories. (A) One Person = 1 person drinking (i.e., a single individual with an alcoholic beverage), (B) More Than One Person = more than 1 person drinking (i.e., 2 or more persons with alcohol beverages), (C) Only Alcohol = alcoholic beverages in isolation, and (D) Nonalcohol = nonalcoholic beverages in isolation.

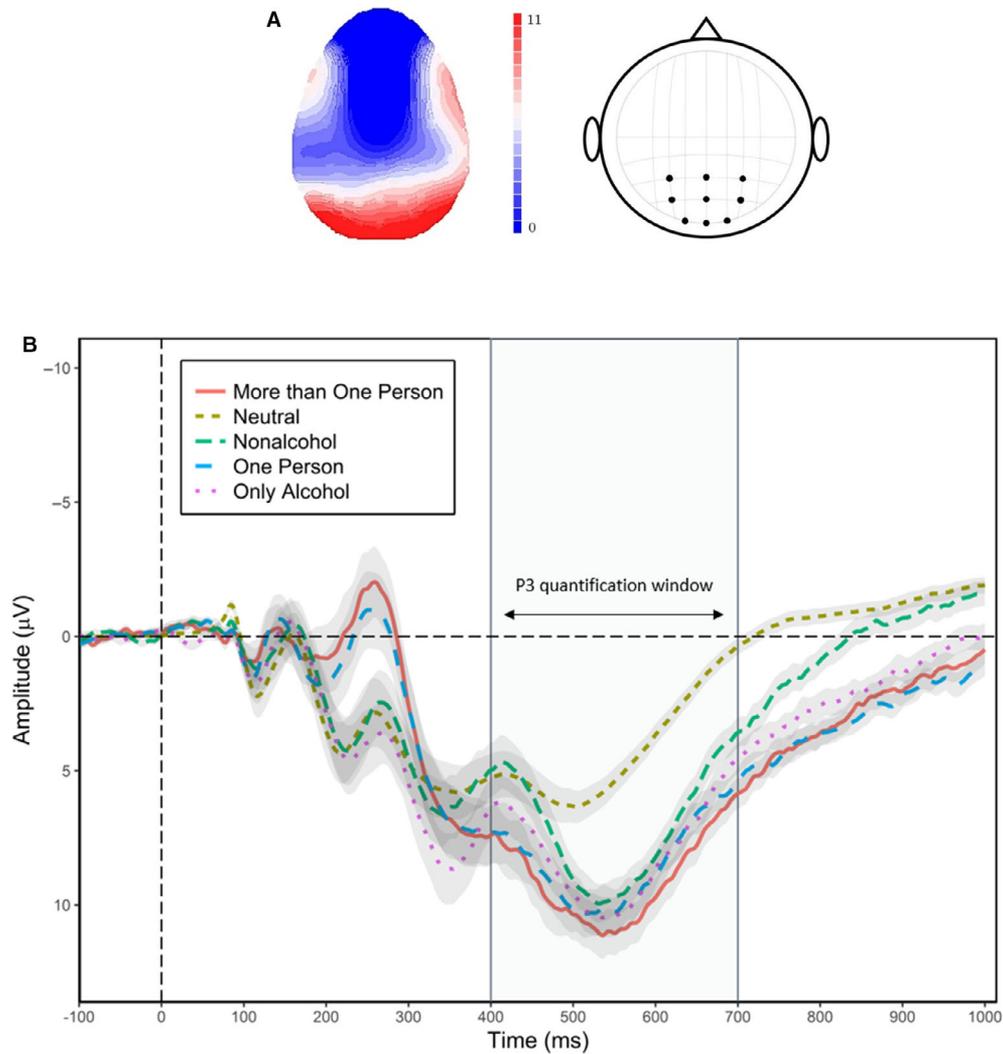


Fig. 2. Panel (A) The topographic distribution of the P3 component of the event-related potential (ERP) and display of the electrodes (P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2) used for quantifying P3 amplitude. Panel (B) Grand-averaged waveforms per image type. Waveforms represent averaged amplitudes across electrodes P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2. Shaded areas around lines depict standard errors. Vertical lines delimit the measurement window (300 to 700 ms) used for P3 amplitude quantification.

horizontal or saccadic eye movements. Scalp recording sites were referenced online to the right mastoid; an average mastoid reference was derived offline. Scalp impedances were kept below 5 k Ω . The EEG was sampled at 500 Hz using a Neuroscan Synamps amplifier (Compumedics Neuroscan, Charlotte, NC) and filtered online at 0.05 to 40 Hz. Eye blinks were removed from the EEG signal offline using a regression-based procedure (Semlitsch et al., 1986), after which stimulus-locked epochs of 1,100 ms were derived from the EEG. Epochs were then baseline-corrected (100 ms prestimulus interval) and inspected for artifacts; trials containing voltage deflections of ± 75 microvolts (μV) were rejected. Noisy (i.e., unacceptable high impedances) electrodes were marked as bad, and data from those electrodes were excluded from the analyses (<1%).

The electrode sites and measurement window for quantifying P3 amplitude were informed by previous studies that have used this paradigm (Bartholow et al., 2007, 2010; Piasecki et al., 2017), as well as by visually inspecting the grand-averaged waveforms collapsed across participants and image types. For each image type, the P3 was quantified by averaging stimulus-locked EEG activity (i.e., the ERP) occurring 400 to 700 ms

poststimulus for each trial at electrodes P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2 (Fig. 2).¹

Procedure

At the beginning of fall and spring semesters, students taking Introductory Psychology completed a web-based survey, which included past-year drinking quantity and frequency items as well as items from the brief drinking motives questionnaire (Kuntsche and Kuntsche, 2009). Students who met criteria for study inclusion based on their responses were then contacted through e-mail with information about the study and a code they could use online to sign up for an individual laboratory session.

After arriving at the laboratory, participants provided informed consent and then were fitted with an electrode cap. Following

¹We also quantified the late positive potential (LPP) as the average amplitude occurring 700 to 1,000 ms poststimulus; results from ancillary analyses using the LPP amplitudes are presented in the Supplementary Materials.

Table 1. Summary of Descriptive Statistics and Reliability of the Self-Reported Measures Used in the Study

	<i>N</i>	Mean (SD)	α
Alcohol variables			
Quantity alcohol use, past 12 months	80	5.23 (2.87)	–
Frequency alcohol use, past 12 months	80	1.35 (1.33)	–
AlcQF, past 12 months	80	9.21 (14.11)	–
Alcohol sensitivity—Light	80	3.59 (1.25)	0.90
Alcohol sensitivity—Heavy	77	7.22 (3.13)	0.95
Valence ratings			
Nonalcohol [NA]	80	6.62 (1.17)	0.64
Only Alcohol [OA]	80	5.43 (1.39)	0.84
One Person Drinking [OP]	80	3.66 (0.99)	0.81
More Than One Person Drinking [MP]	80	5.20 (1.36)	0.79
Arousal ratings			
Nonalcohol [NA]	80	4.18 (2.00)	0.88
Only Alcohol [OA]	80	3.80 (1.51)	0.89
One Person Drinking [OP]	80	3.36 (1.49)	0.88
More Than One Person Drinking [MP]	80	4.36 (1.56)	0.80
P3 amplitudes			
Nonalcohol [NA]	80	7.01 (4.95)	0.81 ^a
Only Alcohol [OA]	80	7.79 (4.76)	0.83 ^a
One Person Drinking [OP]	80	8.42 (4.66)	0.82 ^a
More Than One Person Drinking [MP]	80	9.11 (4.97)	0.66 ^a

AlcQF = composite of number of drinks typically consumed per drinking occasion and typical number of drinking occasions (per week) during the past 12 months; Alcohol sensitivity—Light = unstandardized Alcohol Sensitivity Questionnaire (ASQ) scores for the lighter-drinking ASQ factor; Alcohol sensitivity—Heavy = unstandardized ASQ scores for the heavier-drinking ASQ factor; SD = standard deviation.

^aReliability estimates for the P3 measures are based on split-half reliabilities averaged across 9 electrodes (P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2).

electrode placement and testing, participants completed the alcohol picture-viewing task while EEG was recorded. After the picture-viewing task, participants completed SAM ratings of the beverage images and a computerized survey (Qualtrics, Inc., Seattle, WA), including the ASQ among other measures (see Appendix S1 for a detailed description of the other measures used). The electrode cap was then removed, and participants were shown to a private restroom (equipped with a shower) to wash the electrode gel from their face and hair. Finally, participants were debriefed about the nature of the study and its hypotheses and were dismissed. The University of Missouri Institutional Review Board approved the methods and materials used in this study.

Data Analytic Approach

Data analyses involved the estimation of a series of linear mixed-effects models (LMMs) in IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Armonk, NY). LMMs address limitations of traditional repeated-measures ANOVA (*r*ANOVA) for analyzing dependency in psychophysiological data in within-subjects designs (e.g., Page-Gould, 2017; Volpert-Esmond et al., 2017). In particular, LMMs allow selection of the most appropriate variance-covariance structure for repeated effects to differentially reflect idiosyncrasies of psychophysiological data featuring nonindependent or correlated errors, thus violating the conditional independence and sphericity assumptions. In addition, LMMs include individuals for whom part of the data is missing, thus maximizing the power of a given dataset. Likewise, by using “partial pooling” or shrinkage, unbiased and sensible parameter estimates can be obtained from unbalanced data or designs and be less influenced by outlier observations. Finally, LMMs allow the specification of clusters in the data and the estimation of random effects, which controls

for inappropriate type I error rates and improves the generalizability of results (Barr et al., 2013; Page-Gould, 2017; Volpert-Esmond et al., 2017).

Model building followed the “maximal model” approach, including virtually all possible random effects justified by the design (see Barr et al., 2013). Log-likelihood ratio tests then were used to select the appropriate random effects supported by the data using a significance level of $p < 0.2$ (see Matuschek et al., 2017). All between-person, continuous predictor variables were grand-mean-centered (Enders and Tofghi, 2007). Given evidence of dramatic age and sex differences in P3 amplitudes (e.g., Petit et al., 2013), initial models statistically adjust for participant-level, time-invariant covariates, such as participants’ age and sex; whenever these variables did not account for significant variance, they were removed from the final estimated models. Final models were estimated using the restricted maximum likelihood (REML). The significance of individual fixed-effect (unstandardized weights) parameters was tested using approximate *t*-tests and 95% confidence intervals (CIs) for which the denominator degrees of freedom were obtained with Satterthwaite approximation method.

RESULTS

Descriptive Analyses

Table 1 summarizes the descriptive statistics and reliability estimates of the self-report measures. As expected, and largely consistent with previous work (Fleming et al., 2016), the ASQ-L and ASQ-H scores were highly correlated ($r = 0.71$, $p < 0.001$) and both scales were positively associated with typical weekly alcohol use in the past year, but the associations were small-to-moderate in magnitude ($r = 0.28$, $p = 0.01$ and $r = 0.23$, $p = 0.047$, respectively). Results from ancillary analyses of the behavioral categorizations (“pleasant” vs. “neutral”) during the picture-viewing oddball task can be found in the Appendix S1.

Primary Hypotheses

Figure 2 shows the grand-averaged waveforms for each image category. Figure 3 shows grand-averaged waveforms as a function of image category and levels of alcohol sensitivity (median splits of ASQ-H and ASQ-L, for presentation purposes only).

ACR-P3 and Alcohol Sensitivity. To test the hypothesis that ASQ-L and ASQ-H scores would be associated with enhanced ACR-P3 but not P3 reactivity to nonalcohol cues, we submitted P3 responses to a cross-classified linear mixed-effects model. The fixed effects included the main effects of ASQ-L and ASQ-H scores and image category (OA and NA categories), as well as 2-way interactions involving ASQ-L and ASQ-H scores with image category, controlling for sex, age, and AlcQF. The crossed random effects included both a random intercept and random within-slope of image category varying by participant and a random intercept varying by electrode with a structure for random effects allowing for the specification of heterogeneous variances, but not covariances among random effects.

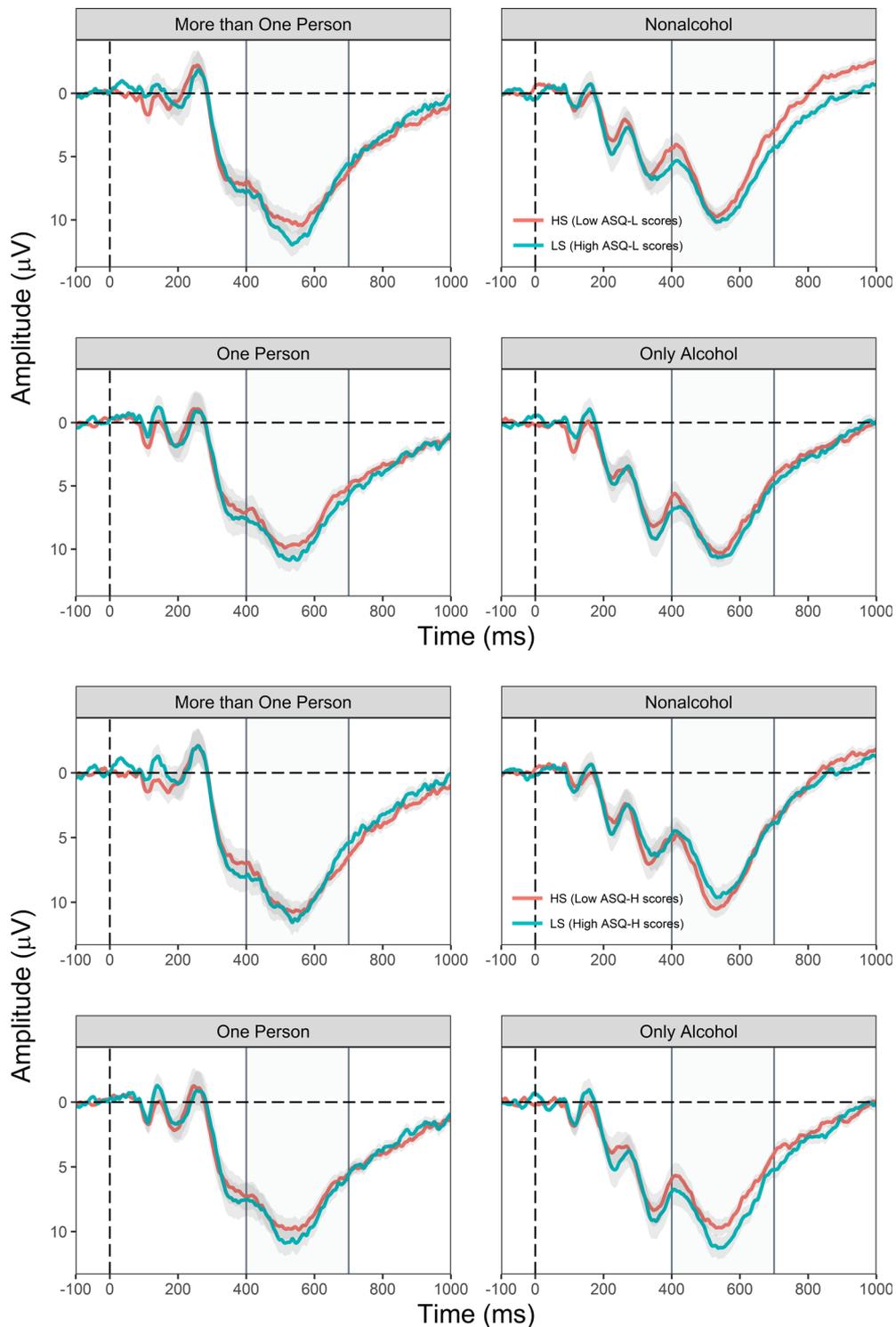


Fig. 3. Grand-averaged waveforms elicited by each of the 4 beverage image types, as a function of the levels of alcohol sensitivity to lower-dose/stimulating alcohol's effects (ASQ-L) and higher-dose/sedating alcohol's effects (ASQ-H); HS = high sensitivity; LS = low sensitivity (a median split of either ASQ-L or ASQ-H scores was used to define HS and LS groups for the purpose of displaying the waveforms; continuous ASQ-L and ASQ-H scores were used in all relevant analyses). Waveforms represent averaged amplitudes across electrodes P3, Pz, P4, PO3, POz, PO4, O1, Oz, and O2. Shaded areas around plotted lines depict standard errors. Solid vertical lines delimit the measurement window (300 to 700 ms) used for P3 quantification. ASQ, Alcohol Sensitivity Questionnaire.

This model produced a significant ASQ-H \times Image category interaction, $F(1, 73.774) = 5.14, p = 0.026$. Inspection of Fig. 4 shows that ASQ-H scores showed opposing

associations with OA and NA images, although neither simple slope was statistically significant. Specifically, ASQ-H was positively associated with the P3 elicited by OA images,

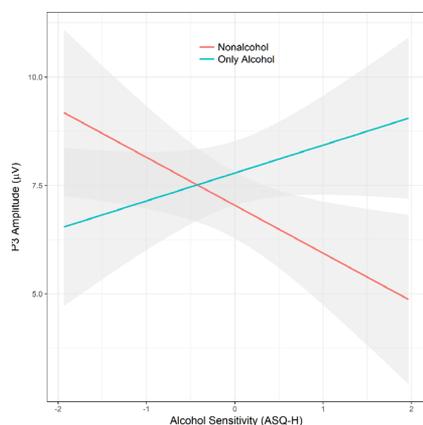


Fig. 4. Display of the 2-way interaction of alcohol sensitivity (ASQ-H) \times image type (Only Alcohol and Nonalcohol) on P3 amplitude. Shaded areas around lines represent standard errors. ASQ, Alcohol Sensitivity Questionnaire.

($b = 0.64$, $SE = 0.86$, $t[73.096] = 0.75$, $p = 0.459$, 95% CI $[-1.08, 2.36]$), whereas ASQ-H was negatively associated with P3 amplitudes elicited by NA images ($b = -1.10$, $SE = 0.91$, $t[72.886] = -1.21$, $p = 0.229$, 95% CI $[-2.92, 0.71]$). No other main or interaction effects were significant in this model.

ACR-P3, Alcohol Sensitivity, and People Drinking. Another question examined in the current study was whether associations between alcohol sensitivity and ACR-P3 are potentiated when images depict people drinking alcohol. We predicted that ASQ scores would be more strongly related to ACR-P3 elicited by images of people drinking than of alcohol cues in isolation. This hypothesis was tested with a cross-classified linear mixed-effects model. The fixed effects included main effects of ASQ-L and ASQ-H and image category, here comparing OA with a combined “people drinking” category (collapsing the OP and MP categories), along with the relevant 2-way interactions, controlling for sex, age, and AlcQF. The crossed random effects included both random intercept and random within-slope of image category varying by participant and a random intercept varying by electrode with a structure for the random effects allowing for the specification of heterogeneous variances, but not for covariances among random effects.

This model produced a significant main effect of image category, $F(1, 73.838) = 6.42$, $p = 0.013$. As expected, images containing people drinking in naturalistic environments ($M = 8.705$, $SE = 0.769$) elicited larger ACR-P3 than images of alcohol beverages devoid of social context ($M = 7.759$, $SE = 0.781$). No other main or interaction effects were significant. However, this model produced a marginally significant ASQ-H \times Image category interaction, $F(1, 73.692) = 3.22$, $p = 0.077$. Contrary to our expectations, however, inspection of the simple slopes suggested the interaction was driven by an unexpected negative

association between ASQ-H scores and ACR-P3 elicited by “people drinking” images ($b = -0.42$, $SE = 0.83$, $t[73.086] = -0.51$, $p = 0.612$, 95% CI $[-2.09, 1.24]$). This pattern opposes the positive association between ASQ-H scores and ACR-P3 amplitude elicited by OA images reported previously. In other words, ACR-P3 amplitudes elicited by OA and “people drinking” image types were differentially associated with ASQ-H scores.

ACR-P3, Alcohol Sensitivity, and Social Context Versus Private Context. Finally, we tested whether ASQ-L and ASQ-H scores were differentially associated with ACR-P3 responses to alcohol-related images according to their social contexts (i.e., multiple people drinking in social settings versus people drinking alone in more private settings). To test this possibility, we tested a cross-classified linear mixed-effects model including main effects of ASQ-L and ASQ-H scores, as well as valence (positive and negative) and image category (OP and MP), along with the relevant 2-way interactions, controlling for sex, age, and AlcQF. The crossed random effects included both random intercept and random within-slope of image category by valence varying by participant and a random intercept varying by electrode with a structure for the random effects allowing for the specification of heterogeneous variances, but not for covariances among random effects.

This model produced a small but statistically significant main effect of AlcQF ($b = -0.08$, $SE = 0.04$, $t[72.531] = -2.03$, $p = 0.047$, 95% CI $[-0.15, -0.001]$). The model also produced a main effect of valence, $F(1, 205.245) = 7.505$, $p = 0.007$, suggesting that, on average, positive images elicited larger P3 amplitudes ($M = 9.289$, $SE = 0.816$) than negative images ($M = 8.179$, $SE = 0.820$). The model did not produce any other statistically significant main or interaction effect at the conventional significance level of $p < 0.05$. The ASQ (i.e., ASQ-L and ASQ-H) effects did not vary systematically as a function of image type (i.e., OP vs. MP).

Ancillary analyses were conducted to test whether there was any systematic difference in P3 amplitude as a function of image valence. P3 amplitudes were submitted to a cross-classified linear mixed-effects model. The fixed effects included the main effect valence of the images (positive vs. negative), as well as image category (OP and MP), along with all 2-way interactions of image valence \times image category, controlling for sex, age, and AlcQF. The crossed random effects included a random intercept and random within-slope of image valence by image category varying by participant and a random intercept varying by electrode with a structure for random effects allowing for the specification of heterogeneous variances but not for covariances among random effects. This model produced only a significant main effect of valence, $F(1, 214.096) = 7.205$, $p = 0.008$. No other reliable main or interaction effects were observed. Therefore, valence did not differentially affect P3 amplitude within image categories (OP and MP) in the current study.

DISCUSSION

Previous research has consistently shown that LS to alcohol, as assessed via retrospective self-report, is associated with enhanced reactivity to alcohol-related cues both in the laboratory (Bailey and Bartholow, 2016; Bartholow et al., 2007, 2010; Fleming and Bartholow, 2014; Shin et al., 2010) and in the natural environment (Trela et al., 2018). The purpose of the current study was to examine the extent to which variability in 2 alcohol sensitivity phenotypes (i.e., enhanced sensitivity to lower-dose/stimulation-like effects and blunted sensitivity to higher-dose/sedation-like effects) is differentially associated with enhanced ACR-P3, as well as whether this reactivity varies according to the contexts in which cues are presented. Based on previous empirical work indicating that differential sensitivity confers the greatest AUD risk (King et al., 2011a, 2011b, 2014), we predicted that ASQ scores reflecting differential sensitivity would be associated with the greatest ACR-P3. The results partially supported this prediction, in that ASQ scores reflecting sensitivity to higher-dose/sedation-like effects (ASQ-H) were differentially associated with ACR-P3 and P3 reactivity to nonalcohol cues. That is, ASQ-H was positively associated with ACR-P3 amplitude but was negatively associated with P3 amplitude elicited by nonalcohol cues. By separately examining associations between alcohol sensitivity phenotypes (i.e., ASQ-L and ASQ-H scores) and ACR-P3 amplitudes, the current findings help to clarify previous results demonstrating that LS, as determined by a combined score on the ASQ (i.e., overall or general sensitivity), is associated with enhanced ACR-P3 amplitude (Bartholow et al., 2007, 2010).

By extension, the current findings suggest that blunted sensitivity to higher-dose/sedation-like effects might be particularly associated with heightened susceptibility to incentive salience sensitization (see Flagel et al., 2009; Robinson et al., 2014) and enhanced attribution of incentive salience to alcohol-related cues (e.g., Witteman et al., 2015). Although the specific mechanism(s) behind this association remain unclear, blunted sensitivity could be associated with exaggerated incentive salience sensitization for at least 2 reasons. First, at a given dose of alcohol individuals with blunted sensitivity to higher-dose/sedation-like effects might experience the drug's reinforcing and rewarding effects more acutely than its negative and unpleasant effects. Consistent with this idea, some previous researches showed that, when the amount of alcohol consumed on a given occasion is statistically equated across individuals, those people with reduced sensitivity to higher-dose/sedation-like effects of alcohol are less likely to experience hangovers (Piasecki et al., 2012). Similarly, Hone and colleagues (2017) reported that, when equating participants on the typical amount of alcohol they consumed, LS women were less likely than their HS peers to experience alcohol-related sexual situations they later regretted. Given that incentive salience sensitization is thought to occur via reward learning mechanisms (see Berridge and Robinson, 2016), and that attribution of incentive salience appears to

depend on the relative reward value of specific reinforcers (see Patitucci et al., 2016), the diminished likelihood of experiencing negative consequences at a given level of alcohol exposure would be expected to produce greater reward anticipation from alcohol-related cues among LS drinkers and, hence, larger ACR.

In addition, it is also possible that because individuals with blunted sensitivity to higher-dose/sedation-like effects of alcohol feel less intoxicated at a given alcohol dose (see Fleming et al., 2016), they fail to experience a signal to stop drinking and, hence, achieve higher levels of intoxication. Such higher levels of intoxication could potentiate and accelerate sensitization of neural mesolimbic dopamine circuits to alcohol-related cues, facilitating stronger ACR.

Of importance, the current findings can have practical implications for both prevention and treatment of heavy drinking and AUD, in that individuals with blunted sensitivity to higher-dose/sedation-like alcohol's effects may benefit more from certain types of interventions or treatment than others. For example, assuming that individuals with blunted sensitivity to higher-dose/sedation-like alcohol's effects might be particularly vulnerable for enhanced attribution of incentive salience to alcohol-related cues, these individuals may, as result, experience stronger desires and urges, even when cutting down from drinking. In these cases, pharmacological-based therapeutic interventions based on medications for reducing urges and cravings for alcohol, such as *naltrexone*, may prove to be effective treatments of heavy drinking and AUD.

A second question addressed in the current study was whether associations between the 2 alcohol sensitivity phenotypes and ACR-P3 would be potentiated when alcohol cues are depicted with people drinking. In general, it was predicted that ACR-P3 would be most pronounced for images including people drinking in naturalistic drinking contexts, especially among participants reporting differential alcohol sensitivity. Contrary to this prediction, pictures representing people drinking, whether alone or in groups, did not potentiate the effects of the 2 alcohol sensitivity phenotypes on ACR-P3. In fact, if anything, a marginally significant ASQ-H \times Image category interaction suggests that sensitivity to higher-dose/sedation-like alcohol effects was negatively associated with ACR-P3 elicited by "people drinking," but positively associated with ACR-P3 elicited by alcoholic beverages in isolation. Although a number of lines of evidence led us to predict positive associations with both of these cue types, considering additional previous research suggests, however, some potential explanations for this unexpected pattern. In particular, it seems likely that in images of people drinking in naturalistic contexts, alcohol cues are a less prominent feature of the depicted scene (see Miller and Fillmore, 2010). The relative prominence of people in such images likely emphasizes the social interaction or emotional tone of those scenes, effectively downplaying the alcohol content. This is relevant because, for heavy and at-risk drinkers, the incentive value of natural reinforcers such as social

interaction becomes weaker as the incentive salience of alcohol-related reinforcement increases (Goldstein and Volkow, 2011; MacKillop et al., 2010a, 2010b; Murphy and MacKillop, 2006). The finding that ASQ-H scores were (somewhat) negatively associated with ACR-P3 amplitude elicited by the “people drinking” images but positively associated with OA images is consistent with this idea.

Findings from some previous studies testing effects of cue context, including the presence versus absence of people, on other indices of cue reactivity lend some support for this idea (see Forestell et al., 2012; Miller and Fillmore, 2010). The studies by Forestell and colleagues (2012) and Miller and Fillmore (2010) are particularly relevant for interpreting the dissociation between ASQ-H scores and ACR-P3 elicited by images containing people versus no people. In their 2012 study, Forestell and colleagues (2012) used a dot-probe task in which targets were presented in hemifields previously containing alcohol or nonalcohol cues alone (inactive condition) or depicting people interacting with them (active condition). The researchers also manipulated cue duration (500 ms vs. 2,000 ms). Their results showed that, among at-risk drinkers, cues presented for a longer duration were associated with an attention bias for alcohol, but only for the inactive condition. In other words, cues depicting alcohol alone were better at capturing at-risk drinkers’ attention than cues depicting people interacting with alcohol when the cues were presented for a relatively long duration. Similarly, Miller and Fillmore (2010), using a modified visual-probe task, obtained reaction-time and eye-tracking (i.e., fixation times) measures of attentional bias measures to alcohol cues varying in image complexity—that is, images containing naturalistic drinking scenes with people drinking alcohol (complex images) and images of alcohol beverages alone (simple images). Findings suggested that, among regular, moderate-to-heavier drinkers, attentional bias, as indexed by both measures used, was elicited by simple but not complex images.

Relative to previous studies (Bartholow et al., 2007, 2010; Piasecki et al., 2017), the design and analytic approach of the current study provided a number of advantages for specifying associations between subjective response to alcohol and cue reactivity. Most importantly, the current study was the first to separately estimate associations between 2 theoretically distinct subjective response profiles and ACR-P3 amplitude. Moreover, including scores on both ASQ subscales in each model represents a conservative statistical approach, ensuring that any associations with ACR-P3 amplitude reflect variance uniquely associated with each subscale and not variance shared between the 2 subscales. Additionally, each model also included an alcohol involvement variable (AlcQF), thereby ensuring that associations between alcohol response phenotypes and ACR-P3 were not confounded by different levels of drinking that could affect both sensitivity levels (Martinez et al., 2010; Schuckit and Smith, 2004) and conditioning of alcohol-related cues (Witteman et al., 2015). Finally, inclusion of stimuli representing naturalistic drinking contexts has the potential to enhance the

ecological validity of the findings, a persistent concern about laboratory-based cue-reactivity findings (e.g., Shiffman et al., 2015).

However, the current design also had some limitations that prevent us drawing specific conclusions regarding a number of important factors. In particular, the comparisons that were the focus of the current analyses were based on differing numbers of images across the image categories. Nevertheless, although the imbalanced number of pictures per category is far from ideal, each image was shown frequently enough that each category included at least 20 to 30 usable trials per category, which is sufficient to maintain acceptable signal-to-noise ratio for the P3 in each condition (Cohen and Polich, 1997; Moran et al., 2013). Moreover, the current design did not include images of alcohol cues completely devoid of any naturalistic context. Although we manipulated the number of people in the images (i.e., social context), even the NA and OA images depicted beverages in a natural-looking physical context, such as on a bar or on a restaurant table (see Fig. 1). Thus, we cannot draw any conclusions concerning the effects of the physical setting on ACR-P3 amplitude. The current results replicated previous work (e.g., Weinberg and Hajcak, 2010) in showing that images including people elicit larger P3 responses than images that do not include people, owing to the inherent motivational significance of conspecifics (Franken et al., 2008). Unfortunately, however, none of the stimuli in the current design depicted people drinking nonalcoholic beverages, thereby preventing us from separating effects of social context from effects of beverage contents on ACR-P3 amplitude. In future studies, researchers should systematically vary both the physical context and the social context in which beverages are depicted in order to address these shortcomings of the current design.

The generic nature of the alcoholic beverage images used in the current study could be considered an additional limitation of the study design. Future research should replicate the current results with more naturalistic and idiographic or “personalized” cues (e.g., each participant’s favorite alcoholic beverages) tailored to the specific characteristics of the individuals and effectively representing their unique drinking experiences (see Bartholow et al., 2018; Lovett et al., 2015). Moreover, the OP and MP categories included different numbers of negative and positive target images. Ideally, the design would more carefully balance image valence across categories. However, this imbalance is not problematic per se, given that late positive components of the ERP, such as the P3, are assumed to be modulated by the motivational significance of the stimulus, not by its valence (Begleiter et al., 1983; Franken et al., 2011; Weinberg and Hajcak, 2010; Weinberg et al., 2012). Indeed, ancillary analyses of the current data indicated that although positive images elicited a larger P3 overall than negative images, this effect did not vary systematically across picture categories.

Finally, the finding that ASQ-H scores appeared negatively associated with P3 amplitude elicited by nonalcoholic

beverage cues (see Fig. 4) raises the possibility that P3 reactivity in LS individuals might share some features in common with the blunted P3 profile often observed among people high in externalizing traits (e.g., Nelson et al., 2011; Patrick et al., 2006). Although this possibility is intriguing, unfortunately the design of the current study cannot resolve this question. In future work, it could be important to measure both alcohol sensitivity and externalizing proneness, and to administer both an ACR task and the mental rotation task in which the externalizing-related blunted P3 is typically observed, in order to directly test the similarity between the P3s elicited in both paradigms and their associations with both AUD risk factors.

CONCLUSION

In conclusion, the current study extended earlier evidence linking low alcohol sensitivity to ACR-P3 by examining associations with 2 theoretically distinct alcohol sensitivity phenotypes (see King et al., 2011a, 2011b) and by varying the naturalistic drinking contexts in which alcohol cues were presented. The current findings suggest that (i) the relationship between alcohol sensitivity and ACR-P3 is primarily driven by blunted sensitivity to the higher-dose/sedation-like effects, and (ii) this association emerges for alcohol cues presented without people, but not when the cues depict people drinking. The findings are consistent with the idea that individuals with blunted sensitivity to higher-dose/sedation-like effects might be particularly susceptible to incentive salience sensitization and that enhanced ACR might constitute a potential mechanism or pathway underlying their risk for developing AUD. Additionally, the current findings suggest the possibility that individuals at increased AUD risk due to blunted alcohol sensitivity show reduced reactivity to natural reinforcers, such as social interactions. Future research is required to replicate the results from the current study and to further explore distinct neural and behavioral correlates of 2 theoretically distinct alcohol sensitivity phenotypes and their association with individual differences in ACR and heightened AUD risk.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this research.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Additional self-report measures and ancillary analyses.